REMARKS

Claims 1-13 and 15-25 were pending at the time of the Office Action. Claims 1-13, 15, 18, and 19 stand withdrawn as drawn to non-elected subject matter. Claims 16, 17, and 20-25 stand rejected under 35 U.S.C. § 103(a). Applicants address this rejection below.

Amendments to the Claims

Claims 16 and 17 have been amended to require that the mesenchymal cell be a stem cell and that the viral vector be a Sendai viral vector. Claims 20-25 have been cancelled. Support for the present amendments is found, e.g., on page 13, lines 9-10, and page 17, lines 24-30, of the English-language translation of the specification as filed.

As the present amendments serve to reduce the issues on appeal and do not require further search or consideration, applicants respectfully request that they be entered.

The present amendments were made to expedite prosecution, and applicants reserve the right to pursue any cancelled subject matter in this or in a continuing application. No new matter has been added.

Rejection Under 35 U.S.C. § 103(a)

Claims 16, 17, and 20-25 stand rejected under 35 U.S.C. § 103(a) as being unpatentable over Ueno et al. (U.S. Application Publication No. 2002/0037278; "Ueno")

and Sakai et al. (FEBS Letters 456:221-226, 1999; "Sakai"). Claims 20-25 have been cancelled, and thus the rejection is moot with respect to these claims. Regarding claims 16 and 17, applicants make the following remarks.

In the reply filed on January 31, 2008, applicants provided arguments and directed the Office's attention to evidence in the specification demonstrating superior unexpected results associated with the use of Sendai viral vector as a vehicle for the introduction of Ang-1 into mesenchymal stem cells. In the present Office Action, the Office maintains (page 6) that (a) "the evidence is not commensurate in scope with the claimed invention," (b) "mere recognition of latent properties in the prior art does not render non-obvious an otherwise known invention" (*In re Wiseman,* 596 F.2d 1019, 201 U.S.P.Q. 658 (CCPA 1979), and M.P.E.P. § 2145), and (c) "the substitution of an adenoviral vector for a Sendai virus vector would provide a reasonable expectation of success."

Regarding argument (a), to expedite prosecution, applicants have amended the claims to feature Sendai virus and mesenchymal stem cells. As such, the evidence is commensurate with the scope of the claims, as amended, and this argument is moot.

Turning to argument (b) – namely, the Office's assertion that superior transduction efficiency is merely a latent property of the prior art – applicants respectfully disagree and direct the Office's attention to M.P.E.P. § 2145.II, which teaches: "Prima facie obviousness is not rebutted by merely recognizing additional advantages or latent properties present in the prior art" (emphasis added). In the instant case, the prior art did

not teach or suggest extraordinary gene expression in mesenchymal stem cells by a Sendai viral vector or a significant therapeutic effect on ischemia. These technical effects were not only recognized in the instant invention, but also achieved for the first time. Since the cited portion of M.P.E.P. § 2145.II is directed to additional advantages or latent properties present in the prior art, it is innaposite in the instant case, where the significant property was not present in the past but was achieved for the first time by the instant invention. With respect to *In re Wiseman*, applicants note that the advantage of venting steam or vapor during a braking action was a mere discovery of a latent property which was already and inherently achieved in the prior art, because "[the] prior art...contains the same solution" for a similar problem (see MPEP § 2141.02.III, emphasis added). Therefore, the instant invention is clearly distinct from *Wiseman*.

The Office further asserts that "mere recognition of latent properties in the prior art does not render nonobvious an otherwise known invention" (page 6, second paragraph, emphasis added). However, the property shown in the instant application is not present in the prior art. Rather, the property has been achieved by the present invention for the first time by combining a mesenchymal stem cell and a Sendai viral vector encoding Ang-1 protein. Therefore, the reasoning based on a latent property of a known invention cannot be applied to the present invention.

Applicants submit that the Office has misconstrued *Wiseman* and M.P.E.P. § 2145. In particular, it cannot be correct, as a general principle, that unexpected superior results

exhibited in *prima facie* obvious inventions are necessarily latent properties which naturally flow from the invention. Indeed, in the context of a *prima facie* obviousness rejection, unexpected superior results must be taken into account as secondary considerations of non-obviousness. Applicants again direct the Office's attention to M.P.E.P. § 2145, which states: "Rebuttal evidence may also include evidence that the claimed invention yields unexpectedly improved properties or properties not present in the prior art." Applicants further direct the Office's attention to M.P.E.P. § 716.02(a).I, which states: "'A greater than expected result is an evidentiary factor pertinent to the legal conclusion of obviousness...of the claims at issue.' *In re Corkill*, 711 F.2d 1496, 226 USPQ 1005 (Fed. Cir. 1985)." In addition, M.P.E.P. § 716.02(a).II states: "Evidence of unobvious or unexpected advantageous properties, such as superiority in a property the claimed compound shares with the prior art, can rebut prima facie obviousness." Nothing in either Ueno or Sakai teaches or suggests the extraordinary extent of gene transduction efficiency of mesenchymal stem cells using a Sendai virus vector, as noted in applicants' previous reply. Therefore, the unexpected results of the invention should be considered as evidence of non-obviousness.

In applicants' reply of January 31, 2008, applicants argued that the specification provides evidence of superior unexpected results associated with the use of Sendai viral vector as a vehicle for the introduction of Ang-1 into mesenchymal stem cells. In view of M.P.E.P. § 716.02(a), the evidence presented by applicants in the specification and

previous reply should be sufficient to establish non-obviousness of the instant invention.

With respect to the "latent property" reasoning presented in M.P.E.P. § 2145, applicants direct the Office's attention to *In re Baxter Travenol Labs* (952 F.2d 388, 21 USPQ2d 1281 (Fed. Cir. 1991)), wherein the appellant in that case argued that the presence of DEHP as the plasticizer in a blood collection bag unexpectedly suppressed hemolysis and therefore rebutted any *prima facie* showing of obviousness. Appellant's argument was unsuccessful because the closest prior art utilizing a DEHP plasticized blood collection bag inherently achieved the same result, although this fact was not known at the time (see M.P.E.P. § 2145). While the "latent property" reasoning may be applicable if the same property was inherently achieved in the subject matter which is taught in the prior art, there is no rationale, under the cited legal precedent and sections of the M.P.E.P., for applying such reasoning to a property which was not yet achieved in the prior art. Once again, applicants wish to emphasize that a generalized teaching in Sakai that Sendai virus vectors are useful for efficient replication and gene expression does not render obvious the presently-claimed subject matter – particularly in view of a teaching of superior unexpected results showing a more than one hundred-fold increase in expression in comparison to an adenovirus vector (see, e.g., pages 10-11 of the reply filed on January 31, 2008). An improvement of such magnitude could not have been predicted by one of skill in the art in view of Ueno or Sakai, either individually or in combination.

Furthermore, applicants submit that the art cited by the Office not only fails to

identify transfection of mesenchymal cells as a "problem" but further fails to associate improved transfection efficiency with Sendai viral vectors in particular. The instant invention is not merely the result of passive observation but instead results from extensive study and intentional selection based on the insight of the inventors, from among the myriad of possible options, of a specific combination of vector (SeV), gene (Ang-1), and cell (mesenchymal stem cells), and the subsequent remarkable discovery of its overwhelmingly superior properties as compared to the cited art. Accordingly, applicants respectfully reiterate that the unexpected superior results already made of record should be taken into account by the Office as objective indicia of non-obviousness.

Even had the inventors' process of invention not been intentional, but rather resulted from a sudden insight or from a fortuituous combination of elements, this would not affect patentability. Indeed, regarding the Office's statement that "In the instant case, no evidence has been provided demonstrating that the Sendai virus has been intentionally modified to achieve the observed superior transduction efficiency..." applicants direct the Office's attention to 35 U.S.C. § 103(a), which states: "Patentability shall not be negatived by the manner in which the invention was made." That is to say, under the patent statute, the manner of invention – e.g., whether or not intentionality was present at the time of invention – is immaterial to the determination of patentability. Thus, the Office should not require evidence of intentionality. Evidence of superior unexpected results is sufficient to rebut the *prima facie* case of obviousness, regardless of the process

by which the inventors arrived at the invention.

With respect to the Office's argument (c), relating to reasonable expectation of success, applicants reiterate that the present invention did not yield results which were to be reasonably expected, but rather yielded superior unexpected results as argued in applicants' previous reply and as pointed out above. Therefore, argument (c) is an inadequate basis for rejection. The same can be said for the Office's statement (page 4) that "the simple substitution of one viral vector for another would have yielded predictable results to one of ordinary skill in the art at the time of the invention." As already noted above, the superior unexpected results achieve by applicants would not have been predictable to one of ordinary skill in the art.

The Office further alleges (page 4) that "a minus-strand RNA viral vector is not considered an essential feature of the invention in light of the disclosure that the foreign gene encoding Ang-1 may also be delivered via non-minus-strand RNA viral vectors, e.g. an adenoviral vector, an adeno-associated viral vector, a retroviral vector, a lentiviral vector, a herpes simplex virus vector, and a vaccinia virus vector (pg 12, lines 8-10)." On this point, applicants' arguments are already of record. In particular, applicants direct the Office's attention to pages 12 and 13 of the reply filed on January 31, 2008, which states:

> While vectors other than minus-strand RNA viral vectors are recited in the specification, the specification does not indicate that the expression level or efficacy of other vectors is comparable to that of minus-strand RNA viral vectors. Rather, the specification states (page 12, lines 26-29, of the specification as filed):

> As shown in the Examples, the minus-strand RNA viral vector could achieve higher expressions of an introduced gene with a lower titer than those of the adenovirus. The Angl-encoding minus-strand RNA viral vector is one of the most preferably used vectors in the present invention.

The specification further states (page 18, lines 10-13):

> In the present invention, minus-strand RNA viral vectors have been found to introduce foreign genes into mesenchymal cells with exceedingly high efficiency. Accordingly, when mesenchymal cells are used in an *ex vivo* administration, it is preferable to use a minus-strand RNA viral vector to introduce genes into the mesenchymal cells.

These teachings, and supporting data, stand in significant contrast with Ueno's preference for a retroviral vector. In any case, all claims, as amended, require a minus-strand RNA viral vector. Thus, based both on the data provided in the specification and on the claims as presently amended, applicants submit that the element of a minus-strand RNA viral vector is an inventive and essential feature of the presently claimed invention.

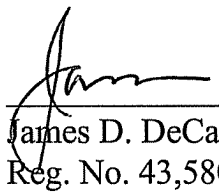
In summary, applicants have addressed each of the Office's arguments with respect to the rejection under 35 U.S.C. § 103(a). In particular, the scope of the evidence in the specification is at least commensurate with the scope of the claims, as amended; the prior art neither teaches nor suggests latent properties which would render the presently-claimed subject matter obvious; and substitution of an adenoviral vector for a Sendai virus vector would not have provided one of ordinary skill in the art with a reasonable expectation of the success that applicants in fact achieved. Accordingly, the rejection of claims 16 and 17 under 35 U.S.C. § 103(a) should be withdrawn.

CONCLUSION

Applicants submit that the claims are in condition for allowance, and such action is respectfully requested. If there are any charges or any credits, please apply them to Deposit Account No. 03-2095.

Respectfully submitted,

Date: 7/25/2008



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